Can obesity in early childhood be influenced by lifestyle interventions during pregnancy? A systematic review of the literature.

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Abstract

Evidence suggests that adverse nutritional exposures during in-utero development may contribute to heightened risk of obesity in childhood. Pregnancy offers the opportunity to modify the intrauterine environment by manipulation of diet and/or physical activity, which may result in favourable health benefits for the child. The objective of this systematic review was to determine whether antenatal lifestyle interventions in pregnant women, aimed at modifying diet and/or physical activity, lead to a reduction in measures of offspring obesity in early childhood. Three electronic databases were searched from January 1990 to July 2017 for antenatal interventions with subsequent offspring follow-up publications. Eight trials were identified. Five trials included women from all body mass index (BMI) categories, three trials included obese women only. Children in the offspring follow-up studies were aged 6 months to 7 years. Measures of adiposity in the offspring (n=1989) included weight, BMI, z-scores, circumferences and skinfold thicknesses. Two studies, focusing on obese women only, reported reduced measures of adiposity (subscapular skinfold thickness and weight-for-age z-score) at 6 and 12 months, respectively. The remaining six studies, two from infancy and four in early childhood found no effect on measures of adiposity.

Measures of obesity up to 12 months of age have been shown to be reduced by antenatal lifestyle interventions during pregnancy in obese women. Due to the heterogeneity of the methodology of the antenatal interventions and the reported offspring outcomes we were unable to draw any conclusion on the influence of antenatal interventions on measures of obesity in early childhood.

Keywords: antenatal intervention; maternal obesity; childhood obesity; developmental origins of disease, body composition

Introduction

The World Health Organization (WHO) have stated that childhood obesity is one of the most serious global public health challenges for the 21st century (WHO, 2016). In the United Kingdom, 24.4% of children aged between two and five years are classified as overweight or obese (van Jaarsveld & Gulliford, 2015). Prevalence rates are also increasing in countries undergoing economic transition where they face the burden of both under and over nutrition (GBD Obesity Collaborators, 2017).

A concerning implication of obesity in children is that once it is established it is difficult to rectify as it tracks into adulthood (Singh et al., 2008). Modelling of growth trajectories from childhood has suggested that the majority of children in the USA (57%) will be obese by the age of 35 (Ward et al., 2017), with half of this projection being established in childhood. However, a recent longitudinal analysis of over 62,000 men living in Denmark suggested that the adverse long-term health effects of childhood overweight can be reversed if weight is normalised prior to puberty (Bjerregaard et al., 2018).

Childhood obesity is a multifactorial condition in which dietary (Ebbeling et al., 2002), environmental (Tremblay & Willms, 2003) and genetic (Aguilera et al., 2013) factors can all play a role. Identification of risk factors and appropriate interventions for the prevention and management of childhood obesity are therefore considered critically important and prevention is a public health priority for countries across the world. There is also a growing body of evidence which suggests that childhood obesity is programmed through exposures during *in utero* development, such as maternal under (Painter et al., 2005) or over-nutrition (Lawlor et al., 2012; Yu et al., 2013), gestational diabetes (GDM) (Ruchat et al., 2013), and excessive gestational weight gain (GWG) (Castillo et al., 2015). It is hypothesised that the *in utero* environment influences critical periods of developmental plasticity resulting in lifelong effects on the offspring and may programme obesity in the child (Gaillard, 2015; Godfrey et al., 2016).

Given the evidence for developmental programming of obesity, antenatal interventions are increasingly utilised as a strategy to prevent childhood obesity. An individual participant meta-analysis of 36 randomised controlled trials (RCTs) recently concluded that diet and physical activity interventions in weight heterogeneous pregnant women can reduce GWG and showed modest improvement in clinical outcomes for both the mother and infant (i-WIP Collaborative Group, 2017). Further, a systematic review which assessed childhood obesity interventions initiated in the first 1000 days of life found that 35% of early life interventions improved childhood weight status, and interventions with the greatest preventive effect should be initiated early in life (Blake-Lamb et al., 2016). Of the studies identified only two studies explored interventions initiated during pregnancy; neither of which had an effect on childhood weight. The current review seeks to expand on this finding by systematically evaluating the impact of dietary and/or physical activity interventions, targeted specifically to the antenatal period, on offspring measures of adiposity in early childhood excluding neonatal measures which reflect directly *in utero* exposures. The review also attempts to define associations between offspring adiposity and 1) the characteristics of the dietary and/or physical activity intervention tested; 2) the method of intervention delivery; 3) the effect of the antenatal intervention on maternal and neonatal outcomes.

Methods

This systematic review was conducted in accordance with the relevant criteria of the PRISMA guidelines for reporting a systematic review (Moher et al., 2009).

Literature search

Three databases were searched for relevant articles, Medline, Embase and Cochrane Central Register of Controlled Trials. The search terms are available in appendix 1, they were adapted for different databases and were limited from 1st January 1990 – 4th July 2017. The first Health and Medical Division (formally, Institute of Medicine) guidelines regarding GWG thresholds were published in 1990, therefore only studies published after 1990 were included in the electronic search to ensure the included publications contained up-to-date knowledge regarding maternal GWG. Reference lists in identified articles, articles cited in relevant reports and review articles were hand searched to identify any additional relevant studies.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were developed using the PICOS (population, intervention, comparison, outcomes and study design) approach summarised in Table 1. Studies were included if they specified: 1) offspring follow-up studies from antenatal RCTs with diet and/or physical activity interventions initiated no later than the second trimester; 2) antenatal RCTs with dietary and/or physical activity intervention in pregnant women with reported BMI and maternal age >15 years according to United Nations classification for women of reproductive age (UNFPA, 2016); 3) offspring follow-up studies which included measures of body composition, including body mass index (BMI), body fat percentage and circumferences; 4) if the age of the offspring at follow-up was between 6 months and 8 years, which is the limit of early childhood as defined by UNESCO (UNESCO, 2016).

For each identified offspring follow-up study the original maternal RCT on which it was based was also analysed for intervention design and outcomes. Antenatal studies were excluded if they were: non-randomised trials, observational studies and cohort analyses of offspring outcomes, studies which included multiple pregnancies. Both follow-up and antenatal studies not published in English were also excluded.

Study selection and data extraction

Following removal of duplicates, titles and abstracts were independently screened against inclusion criteria by two researchers, n=3406 papers were excluded at this stage. The database search identified three maternal lifestyle intervention RCTs which had not yet published follow-up data on their offspring. The authors of these three articles were contacted and the studies were subsequently excluded (Bogaerts et al., 2013; Renault et al., 2014; Thomson et al., 2014). Fifteen studies were assessed for eligibility and the full-text articles were retrieved. Seven studies were excluded with details reported in Figure 1. Data extraction was completed separately and systematically by the same two reviewers and included general characteristics: title, authors, date and place of publication; offspring follow-up: number, method of data collection, measures of obesity, age at follow-up; risk of bias: process of randomisation selection and allocation, loss to follow-up; maternal lifestyle intervention: number and BMI of participant mothers, location, setting, description of intervention (type, duration, frequency).

Data synthesis

For this review the data was synthesised qualitatively, through a narrative summary technique to aid interpretation of trial results. Due to the heterogeneity of the anthropometric measurements used to assess adiposity in the offspring a meta-analysis was precluded. The trials were divided into two groups according to pre-pregnancy BMI data; 1) trials which included women of all categories of BMI (underweight, normal, overweight and obese) and 2) trials in obese women only. As there is a known

association between pre-pregnancy BMI and the development of childhood obesity, by separating the trials by BMI classification this association could be investigated.

Study assessment

The Cochrane Handbook for Systematic Reviews of Interventions tool (Higgins and Altman, 2008) was used to assess the validity and bias of each offspring follow-up publication included. The domains used in this systematic review include: randomisation selection (selection bias), allocation concealment (selection bias) and follow-up of participant drop-out from recruitment to termination of study (attrition bias). Performance bias was not included in the bias assessment due to the nature of the interventions provided. The studies were ranked using high, moderate and low risks of bias, and an overall risk was subsequently determined.

Results

The study identification and selection process for the offspring follow-up studies is presented in Figure 1. A total of 3565 titles were identified in the initial search (Medline 2967, Embase 218, Cochrane 380). Following screening of titles and abstracts, 15 studies were fully assessed for eligibility of which eight met the inclusion criteria. Predominant reasons for exclusion included RCTs that were ongoing and lack of offspring follow-up publications.

The characteristics for the offspring follow-up are summarised in Table 2. Offspring data was collected from a total of 1,989 children, representing 35% to 88% of the offspring available from the antenatal RCTs. The number of offspring investigated from the antenatal studies ranged from 72 to 698. Offspring age at follow-up was 6 months (Horan et al., 2016; Patel et al., 2017), 1 year (Rauh et al., 2015; Vesco et al., 2016), 2.8 years (Tanvig et al., 2014), 4-5 years (Ronnberg et al., 2017) and 7 years (Kolu et al., 2016). The measures of adiposity recorded are described in Table 2, and included anthropometric measurements of weight, height, BMI, circumferences (mid-upper arm, abdominal, hip, thigh), skinfold thicknesses and estimated total body composition values via dual-energy x-ray absorptiometry (DXA) scans.

Offspring measures of adiposity

When reported, anthropometric measures were converted to z-scores and adjusted for infant sex, age and length and standard deviations using WHO growth standards (Horan et al., 2016; Mustila et al., 2012; Patel et al., 2017; Ronnberg et al., 2017; Tanvig et al., 2014; Vesco et al., 2016). Kolu et al. (1016) calculated the children's BMI using a Finnish BMI for age calculator for children aged 2–20 years (Saari et al., 2011). Sums and ratios of anthropometric characteristics as opposed to individual measures were also used to estimate infant adiposity (Horan et al., 2016; Patel et al., 2017; Vesco et al., 2016). Two trials utilised weight changes over time, obtained from multiple measurements to create growth trajectories from birth to 12-months (Rauh et al., 2015) and 2-years (Mustila et al., 2012) of age. One

study (Tanvig et al., 2014) used DXA scans to obtain body composition values from the children, which were completed for <50% of the study population.

Effect of interventions on offspring adiposity

Table 3 shows the effectiveness of lifestyle interventions on offspring anthropometric measures at follow-up. Two RCTs, including obese women only reported significant reductions in offspring measurements of adiposity (subscapular skinfold thickness (Patel et al., 2017) and weight-for-age z-score (Vesco et al., 2016)) between the control and intervention groups. The two trials involved modifying diet and physical activity and both demonstrated a significant reduction in GWG in the intervention arm. In Horan et al. (Horan et al., 2016) participants were recruited on the basis of previous delivery of a large for gestational age (LGA) infant, no significant differences were found in measures of obesity in infants in the intervention arm at 6 months of age compared to the control arm. However, when the data was analysed as a cohort using multiple linear regression modelling, associations between specific maternal dietary variables and infant adiposity, GI, saturated fat and sodium intake in pregnancy were associated with some measures of offspring adiposity at follow-up including weight-for-age z-score, BMI-for-age z-score and select skinfold measurements. Kolu et al. (2016) conducted a separate statistical analysis of a subset that included data obtained from children of women adherent to the lifestyle intervention in the NELLI trial, which included women from all BMI categories. When this subset was analysed, summarised in Table 3, there was a significant reduction in childhood BMI between the intervention and control groups at 7 years of age (n=24, I: 20.5 kg/m^2 vs C: 22.5 kg/m^2, p = 0.04).

Antenatal studies

Characteristics of the eight antenatal interventional studies included are summarised in Table 4. The total sample size for the antenatal interventions was 3,988, which varied by study from 118 to 1555. All interventions were conducted in high-income countries; Denmark (Vinter et al., 2011), Finland

(Kinnunen et al., 2007; Luoto et al., 2011), Germany (Rauh et al., 2013), Ireland (Walsh et al., 2012), Sweden (Ronnberg et al., 2015), UK (Poston et al., 2015) and USA (Vesco et al., 2014). Six trials included a combined dietary and physical activity intervention approach. Walsh et al. (Walsh et al., 2012) included a diet-only intervention and Ronnberg et al. (Ronnberg et al., 2015) included a physical activity only intervention. The study designs included five RCTs (Poston et al., 2015; Ronnberg et al., 2015; Vesco et al., 2014; Vinter et al., 2011; Walsh et al., 2012), two cluster-RCT (Luoto et al., 2011; Rauh et al., 2013) and one quasi-RCT (Kinnunen et al., 2007). Five trials included women from all BMI categories (Kinnunen et al., 2007; Luoto et al., 2011; Rauh et al., 2013; Ronnberg et al., 2015; Walsh et al., 2012) (underweight to obese, these trials did not analyse their results depending on pre-pregnancy BMI), and three included obese women only (BMI ≥30 kg/m^2) (Poston et al., 2015; Vesco et al., 2014; Vinter et al., 2011).

Antenatal intervention

Gestational age at commencement of the antenatal lifestyle intervention ranged from 7 to 21 weeks' gestation. Duration of the intervention varied widely; one RCT involved only a single point of contact for delivery of the intervention (Ronnberg et al., 2015). The most intensive intervention involved participants attending an average of 20±7 (range 0-28) weekly sessions (Vesco et al., 2014). For the seven trials which included a dietary component interventions aimed to reduce glycaemic index (GI) (Poston et al., 2015; Walsh et al., 2012), reinforce existing standard healthy eating guidelines (Kinnunen et al., 2007; Luoto et al., 2011), provide dietary consultations with dietitians to develop personalised diet plans based on standard healthy eating guidelines (Vesco et al., 2014; Vinter et al., 2011) or reduce intake of energy-dense and high-fat foods in order to decrease excessive GWG (Rauh et al., 2013). For the seven trials which included physical activity, the intervention included free fitness club membership (Vinter et al., 2011), verbal encouragement for daily exercises (Rauh et al., 2013; Walsh et al., 2012), trainer-led physical activity sessions (Kinnunen et al., 2007; Luoto et al., 2011), formalised prescription of exercise and regular monitoring of GWG at every anatenatal visit (Ronnberg

et al., 2015) and provision of DVD exercise regimens, a pedometer and logbook, and recommended goals for incremental increases in walking (Poston et al., 2015).

Antenatal controls

Control groups received antenatal care standard for the study setting. This included formal dietary and GWG advice (Walsh et al., 2012) or routine healthy lifestyle advice for the respective country (Kinnunen et al., 2007; Luoto et al., 2011; Poston et al., 2015; Rauh et al., 2013; Ronnberg et al., 2015). One control group was informed about the purpose of study and of a website with healthy lifestyle advice (Vinter et al., 2011), while another received a single dietary advice session immediately after randomisation; this session was routinely covered by the insurance policy of the participating hospital (Vesco et al., 2014).

Outcomes of the antenatal interventions

The maternal and infant outcomes of the intervention are summarised in Table 5. GWG was a primary outcome of five trials (Kinnunen et al., 2007; Rauh et al., 2013; Ronnberg et al., 2015; Vesco et al., 2014; Vinter et al., 2011); all, apart from one (Kinnunen et al., 2007), reported a significant reduction in GWG the intervention arm. The remaining three trials included GWG as a secondary outcome (Luoto et al., 2011; Poston et al., 2015; Walsh et al., 2012), of which two reported a significant reduction in GWG (Poston et al., 2015; Walsh et al., 2012). Three trials included GDM incidence as a primary maternal outcome (Luoto et al., 2011; Poston et al., 2015; Vinter et al., 2011), however none of these reported statistical differences in this outcome between the control and intervention arm. Birth weight, incidence of LGA infants and macrosomia were the primary outcome of four maternal RCTs (Luoto et al., 2011; Poston et al., 2015; Vinter et al., 2011; Walsh et al., 2012), with only one trial showing a significant result (Luoto et al., 2011). Two trials included macrosomic newborns and incidence of LGA as secondary outcomes, both of which were significantly lower in the intervention arm (Kinnunen et al., 2007; Vesco et al., 2014).

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210 **Study quality**

211 The overall quality of the included offspring follow-up studies varied and is summarised in Table 6;
212 two studies were classified as moderate risk (Kolu et al., 2016; Vesco et al., 2016), one as high (Mustila
213 et al., 2012) and the remaining five studies as low risk (Horan et al., 2016; Patel et al., 2017; Rauh et
214 al., 2015; Ronnberg et al., 2017; Tanvig et al., 2014) The main source of bias across all studies was the
215 high rate of participant attrition to offspring follow-up. For the antenatal interventions all of the trials
216 were classified as low risk (Luoto et al., 2011; Poston et al., 2015; Rauh et al., 2013; Ronnberg et al.,
217 2015; Vesco et al., 2014; Vinter et al., 2011; Walsh et al., 2012), except for one trial which was
218 classified as moderate risk (Kinnunen et al., 2007).

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Discussion

The findings of this systematic review, focusing on the impact of antenatal interventions on offspring adiposity, highlight considerable heterogeneity in the methodological design and reported outcomes in the included publications. In two of the publications (n=787) focusing on obese women only, the authors reported reduced measures of adiposity defined as subscapular skinfold thickness and weight-for-age z-score, at 6 and 12 months, respectively. However, the remaining six studies found no effect on measures of adiposity in their offspring. These studies included offspring from 6 months to 7 years. Five trials included women from all BMI categories, and one trial included obese women only.

Antenatal interventions

Considerable variation was found in the study design, recruitment and intensity of the antenatal interventions. For the eight trials identified gestational age at recruitment ranged from 7 to 21 weeks. This variability existed both between (Kinnunen et al., 2007; Walsh et al., 2012) and within the studies (Vesco et al., 2014). Most studies recruited between the end of the first trimester/middle of second trimester. It is plausible that earlier, and thus longer, interventions could have a more pronounced effect on offspring obesity, especially if the intervention commenced prior to conception (Poston et al., 2016). This is suggested by an observational study of siblings born to obese mothers pre- and post-bariatric surgery, in which childhood adiposity was lower in the sibling born after bariatric surgery (Smith et al., 2009). Given that there are potential limitations in initiating interventions in early pregnancy preconception weight loss could be an important strategy in overweight and obese women, although this is may be difficult to achieve due to the high incidence of unplanned pregnancies in developed countries; 45.2% in the UK (Wellings et al., 2013) and 49.0% in the USA (Finer & Zolna, 2011).

Considerable variation was also found in the intensity of the interventions; which mirrors previous reviews (Dodd et al., 2010; Flynn et al., 2016; Oteng-Ntim et al., 2012; Thangaratinam et al., 2012).

246 The number of intervention sessions offered to the mothers varied between 1 to 28. Of the two trials
247 which showed a reduction in infant adiposity Vesco et al. offered weekly group meetings following
248 two individual meetings, each of these sessions lasting up to 90 minutes and on average participants
249 attended 20±7 sessions (Vesco et al., 2014). Poston et al. also showed a reduction in infant adiposity
250 and this was the only study to reach out to mothers who could not attend the prescribed meetings in
251 person, by email or telephone (Poston et al., 2015). This may have contributed to efficacy of the
252 intervention, as a systematic review of technology use in antenatal lifestyle intervention trials has
253 highlighted the benefits of harnessing technology as a tool of delivering the intervention (O'Brien et
254 al., 2014). Adherence to the original study protocol was discussed in three trials; the UPBEAT trial
255 reporting that women completed on average 7 of the 8 sessions provided (Poston et al., 2015) and
256 two other trials, ROLO and the Healthy Moms Trial reported 75% (Walsh et al., 2012) and 80% (Vesco
257 et al., 2014) adherence respectively to the intervention. As mentioned, the follow-up publications
258 (Patel et al., 2017; Vesco et al., 2016) of the UPBEAT (Poston et al., 2015) and Health Moms (Vesco et
259 al., 2014) trials found a significant reduction in measures of adiposity in the offspring at ages 6 and 12
260 months respectively, suggesting that adherence to the antenatal protocol is a likely determinant of
261 effects on infant adiposity.
262
263 **Offspring measures of childhood adiposity**
264 There was significant heterogeneity in the types of offspring measures of adiposity undertaken. There
265 is no ideal measurement of infant or childhood adiposity, and a balance between costs, efficiency, age
266 of the child and ease of collection influences the type of data collected. BMI z-scores or BMI were
267 analysed by five studies and adjusted for infant age and gender and reported as standard deviations
268 (SD) from the median (Horan et al., 2016; Kolu et al., 2016; Patel et al., 2017; Ronnberg et al., 2017;
269 Tanvig et al., 2014). However, BMI is an inaccurate estimate of body fat mass in children, and the same
270 thresholds do not apply as in the adult population. To gain an accurate understanding of body
271 composition in infants and children, other methods such as infant-sized air-displacement

plethysmography (PEAPOD), skinfold thicknesses, DXA and bioelectric impedance analysis (BIA) are more appropriate. PEAPOD and DXA are considered to be the gold standard for measuring body composition for infants and children, respectively. They provide reliable and accurate results for body composition; however they are expensive, requires a trained technician and are time consuming.

Four studies collected skinfold thicknesses or body circumference data (Horan et al., 2016; Patel et al., 2017; Tanvig et al., 2014; Vesco et al., 2016). Both are relatively simple and inexpensive measurements, useful for community paediatrics or large scale studies, and provide information about body fat distribution if measured at various fat depots. However, training is necessary to obtain standardised measurements and they can be poorly reproducible with increasing BMI values in children (Speiser et al., 2005). Subscapular skinfold thickness is recognised as an accurate predictor of central adiposity and it thought to have low measurement error (Mensink et al., 2003). This method was measured in three offspring follow-ups studies (Horan et al., 2016; Patel et al., 2017; Vesco et al., 2016). Patel et al. observed a significant reduction in the intervention arm of the UPBEAT study in both the subscapular thickness z-score and absolute value. The authors conducted a causal mediation analysis which suggested that the change in subscapular skinfold thickness was due to improvements in the antenatal diet and a reduction in GWG (and not postnatal diet). Subscapular skinfold measurements are known to track into obesity in later life and have been associated with adverse metabolic outcomes in adulthood, including impaired glucose metabolism and increased serum cholesterol (Santos et al., 2016; Srinivasan et al., 2003). It therefore should be considered as a standardised, low cost, reliable method for use in future studies.

Tanvig et al. performed DXA scans on the offspring. DXA scans offer an accurate measure of total body fat, and serve as the gold standard for validation of other measures of obesity, however children are required to lie still for 5 minutes and therefore scanning children under the age of 4 years is a challenge (Jensen et al., 2015). Acceptability of a DXA scan by parents, the need to undertake the scan in a hospital setting, and the cost may outway the benefits for this measurement of body composition.

High rates of attrition were observed for six of the follow-up trials. Loss of participants to offspring follow-up may have been affected by the strategy for participant contact. Of the two offspring follow-up studies with the lowest attrition rates, in one, parents were emailed/phoned/mailed to obtain parent-measured data (Mustila et al., 2012). Measurement by untrained parents in this study and not healthcare professionals may have decreased the accuracy and quality of the data, compromising the validity. The second study relied on routinely collected paediatric clinical data, which carries a risk of bias due to the lack of standardised data collection techniques, but with the benefit of lower attrition (Rauh et al., 2015).

Offspring adiposity

Amongst the five RCTs that included women from all BMI categories, none found an effect of the intervention on measures of childhood adiposity. However, of the three studies which followed children of women with a BMI ≥30 kg/m^2, two found that up to 12 months of age, lifestyle interventions influenced infant body composition (Patel et al., 2017; Vesco et al., 2016). Other than an influence of greater adherence to intervention in the UPBEAT trial, this could also suggest a potentially greater influence of the intervention in obese women to improve lifestyle. Alternatively, effects in offspring of obese women might diminish over time, as Vinter et al. (2011) investigated children at 2.5-3.2 years of age and found no significant effects although younger children were not studied. Due to the heterogeneity of the interventions in obese women, the most beneficial intervention design cannot accurately be defined, and accords with the conclusion of Gardner et al. in an earlier review of lifestyle interventions in pregnancy and pregnancy outcomes (Gardner et al., 2011).

Potential biases in the review process

This systematic review has several strengths, including a comprehensive search strategy and compliance with guidelines from the Centre of Reviews Dissemination Systematic Review Guide and the PRISMA statement and checklist. For each offspring follow-up, full-text copies of the corresponding maternal publication were consulted. The review was limited by variability of the studies included, which limited the ability to perform meta-analyses. The possibility of publication bias should be considered because those studies not published in the English language were not included in this systematic review. During the selection of studies for this review, the authors of three antenatal intervention trials which had planned to complete offspring follow-up but had not yet published their results were contacted. Of those who replied, Renault et al. and Bogaerts et al. have recruited exclusively obese women and intend to report childhood outcomes. Results from these studies may enable a more substantive conclusion on the effect of antenatal interventions in offspring of obese women.

High attrition is common in long-term follow-ups of RCTs, and is influenced by multiple factors, including population demography, age at follow-up, nature of methods of outcome measurements and perceived benefit to participants (Fewtrell et al., 2008). For this review, the low number of offspring follow-up data may have diminished the strength of the evidence base. One potential solution to account for missing data is to complete an intention-to-treat (ITT) analysis. ITT analysis includes every subject who is randomized according to randomised treatment assignment. Only three of the included trials utilised this statistical method (Poston et al., 2015; Ronnberg et al., 2015; Vesco et al., 2014). The variation in standard care antenatal practices between the settings and countries of the included studies, could also have influenced the results.

Recommendations for future research and practice

This systematic review included studies with women from all BMI categories. Antenatal interventions were effective at reducing childhood adiposity in obese women only suggesting that analyses of offspring outcomes should potentially be analysed separately for BMI category, although for the smaller studies this would result in limited power. A further limitation was the variability of studies included: the heterogeneity of the antenatal interventions (duration, initiation and components of the intervention) and the variations in offspring methods used to define adiposity was such that a meta-analysis could not be performed. Additionally, ethnicity can impact the development of childhood obesity, and only two trials (Poston et al., 2015; Vesco et al., 2016) included ethnicity data for their participants, one of which stated that it was completed in multi-ethnic populations (Poston et al., 2015).

Future studies should consider standardising the methodological design to that which has been shown to date to be most effective. From this systematic review this would appear to be those in which dietary advice and physical activity was delivered most frequently with high adherence rates. Standardisation of the method of measurement of adiposity in children, which will depend to some extent on the age of the child, should also be considered. This could consist of repeated anthropometric measurements, of height, weight and circumferences, which can be plotted against relevant growth reference charts, therefore growth trajectories and any deviation or crossing of centiles could be observed throughout childhood. These precautions would reduce variability and enable meta-analyses which can contribute to the evidence-based public health guidelines. During the final preparation of this review a protocol was published by the International Weight in Pregnancy Collaboration. The authors, Dodd et al. aim to complete an individual participant data meta-analysis to evaluate the effects of lifestyle interventions in overweight and obese pregnant women, on both maternal outcomes and childhood adiposity at 3-5 years of age. This analysis will be a welcome addition to the field. Furthermore, a recent systematic review investigating interventions during the

first 1,000 days, from conception to two years of age, to prevent childhood obesity reported that individual or family based approaches via the clinical, community and home setting exert a positive effect on child growth (Blake-Lamb et al., 2016). Future studies, including antenatal interventions should consider such approaches to facilitate improve intervention engagement, retention and standardised approaches to follow-up in the post-natal period. These approaches, combined with system levels interventions, may offer a supportive environment to foster sustained behaviour change to improve obesity risk in childhood and, potentially, through the life-course.

Conclusion

A large body of observational evidence proposes an association between the *in-utero* nutritional environment and offspring obesity, although some studies show no association. RCTs have the potential to determine causality. This systematic review highlights the need for appropriately powered, well designed, follow-up trials of antenatal lifestyle interventions in pregnant women, specifically in those with obesity, amongst whom the interventions may have the most significant influence on childhood adiposity. The absence of RCTs with comparable methodological design and low attrition rates limit the ability to recommend a specific lifestyle change for gestational prevention of offspring obesity.

Key messages

- We know from observational data that obesity in children is associated with exposures to nutritional excess in early life, including the in-utero environment. However, to prove causality randomised controlled trials are required.
- Improving antenatal care, through modifying diet and/or physical activity, may reduce offspring obesity.

- Long-term follow-up of children from antenatal lifestyle interventions will help inform the public health policy focusing on maternal health.
- From this systematic review lifestyle interventions during pregnancy in obese women have been associated with reduced measures of obesity in infants up to 12 months of age.
- However, the influence of these interventions on early childhood are currently unknown.

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Table 1: Summary of PICOS criteria for the inclusion of follow-up studies from antenatal dietary and lifestyle interventions

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Table 5: Impact of antenatal lifestyle intervention on primary and secondary outcomes of the antenatal RCT

Table 6: Sources of bias in offspring follow-ups following antenatal lifestyle interventions

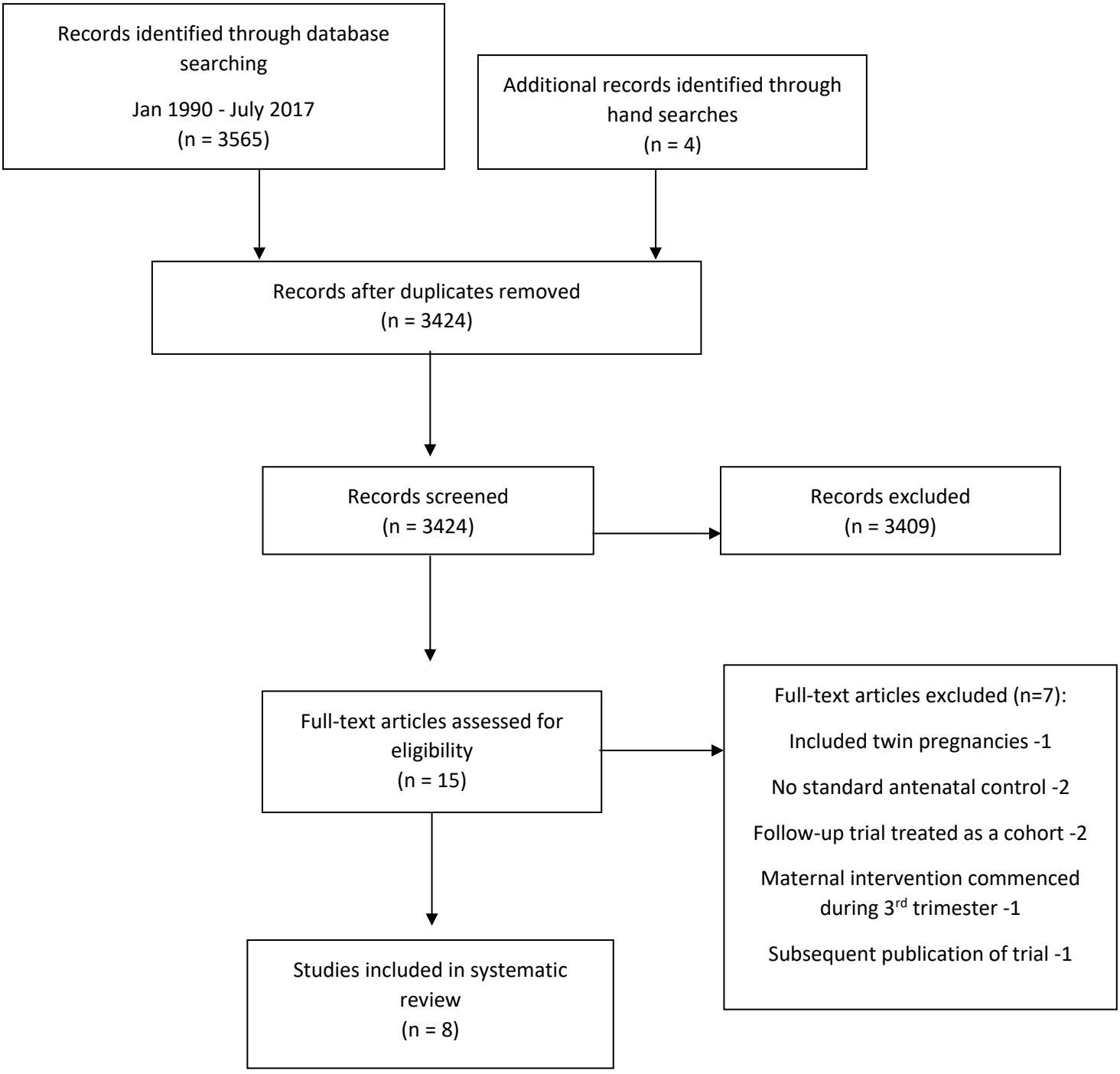

Figure 1: Flowchart of study selection in accordance with PRIMSA guidance

Table 1: Summary of PICOS criteria for the inclusion of follow-up studies from antenatal dietary and lifestyle interventions

Parameter	Description
Population	Pregnant women, >16 years, with detailed pre-pregnancy or first trimester BMI data
Intervention	Diet and/or physical activity
Comparison	Standard antenatal care
Outcomes	Offspring body composition measures from 6 months – 7 years of age
Study design	Randomised controlled trials

BMI, body mass index

Table 2: Offspring follow up of children born to mothers whom received an antenatal lifestyle intervention

Antenatal study	Follow-up study	Follow-up participants (% of antenatal sample)	Age of children at follow-up	Anthropometric outcomes	Breastfeeding rates between control and intervention arm
				All BMI categories	
Walsh et al (2012)	Horan et al. (2014)	n=280 (35%)	29 ± 13.14 weeks	Anthropometric measurements recorded in both follow-ups: weight, length, circumferences (MUA, abdominal, hip and thigh), skinfold data (subscapular, triceps, biceps and thigh).	Not reported
Rauh et al. (2013)	Rauh et al. (2015)	N=220 (88%)	6^{th}-7^{th} month & 10^{th}-12^{th} month	Weight, recorded by paediatrician in an infant health record.	No significant difference
Kinnunen et al. (2007)	Mustila et al. (2012)	n= 72 (66%)	0-48 months	Weight development of the offspring: weight-for-length z score (0-48 months), BMI z-score (24-48 months).	No significant difference
Ronnberg et al. (2014)	Ronnberg et al. (2017)	N=300 (80.2%)	5 years	BMI and BMI z-scores.	No significant difference
Luoto et al. (2011)	Kolu et al. (2016)	n=173 (43.4%)	7 years	BMI*.	Not reported
				Obese only (BMI ≥30 kg/m^2)	
Poston et al. (2015)	Patel et al. (2017)	n=698 (45.9%)	4-8 months	Infant skinfold data (subscapular and triceps), weight, length, abdominal and MUA circumferences. WHO growth standards were used to convert the infant measurements to z-scores which were adjusted for infant age and gender. Estimated total body fat percentage was calculated using skinfold measurements.	No significant difference
Vesco et al. (2014)	Vesco et al. (2016)	n=89 (78%)	12 ± 3 months postpartum	Weight, length, skinfold data (triceps and subscapular) and z-scores	Not reported
Vinter et al. (2011)	Tanvig et al. (2015)	n=157 (52.2%)	2.5-3.2 years	Abdominal circumference, weight and height, skinfold thickness data (triceps and subscapular) and DXA. BMI Z-scores were adjusted for age and sex-specific Danish standards.	No significant difference

BMI, body mass index; DXA, Dual Energy X-ray; MUA, mid-upper arm; SD, standard deviation; WHO, World Health Organisation. * Children's BMI were calculated using a Finnish BMI for age calculator for children aged 2–20 years (Saari et al. 2011).

Table 3: Impact of antenatal lifestyle intervention on offspring adiposity at follow-up

Antenatal study	Follow-up study	Childhood outcomes	Additional results
All BMI categories			
Walsh et al (2012)	Horan et al. (2016)	At 6 months, no difference in any of the infant anthropometric measured between the C and I groups. Including BMI, skinfold thicknesses, z-scores and circumferences	Associations were observed between maternal dietary intake and GI during pregnancy and offspring adiposity at 6 months of age.
Rauh et al. (2013)	Rauh et al. (2015)	After adjustments no difference in weight at follow-up at 10-12 months of age C:9736g ± 999 vs I:9382g ± 931, p = 0.099.	Among women receiving lifestyle counselling, only 8% retained more than 5 kg, while 17% in the control group retained >5 kg. For the whole cohort, an association between higher GWG and increased 12-month weight retention was found (0.4 kg weight retention per 1 kg increase in GWG, p<0.001).
Kinnunen et al. (2007)	Mustila et al. (2012)	The antenatal lifestyle intervention did not reduce weight gain among the offspring (95% CI-0.025 to 0.009, p=0.34).	
Ronnberg et al. (2014)	Ronnberg et al. (2017)	No difference in mean BMI z-scores at age 5, C: 0.26 vs I:0.34, p=0.510.	Maternal obesity was an independent risk factor for offspring obesity at age 5 (OR=4.81, p=0.006).
Luoto et al. (2011)	Kolu et al. (2016)	No difference in BMI* of children at 7 years (C: 22.5kg/m^2 vs I: 21.3kg/m^2, p = 0.07).	For children with mothers classified in the adherent group BMI* was lower (n=24, C: 22.5 kg/m^2 vs I: 20.5 kg/m^2, p = 0.04). Adherent group: during pregnancy mothers fulfilled at least 3/5 dietary aims and/or their self-reported PA exceeded 800 MET/mins per week and their BMI did not exceed their BMI specific limits).
Obese only (BMI ≥30 kg/m^2)			
Poston et al. (2015)	Patel et al. (2017)	Subscapular skinfold thickness z-score was 0.26 SDs (-0.49 to -0.02) lower in the intervention arm (p=0.031). Infants in the intervention arm had a 5% lower subscapular skinfold thickness (mm) (p=0.021)	Causal mediation analysis suggested that lower infant subscapular skinfold thickness was mediated by changes in antenatal maternal diet and GWG rather than postnatal diet. Maternal dietary GL (p<0.001) and SFA (p<0.001) intake were reduced in the intervention arm at 6 months postpartum.
Vesco et al. (2014)	Vesco et al. (2016)	There was a significant main effect of group for infant weight-for-age z-scores (b=-0.40, 95% CI: -0.75 to -0.05; p=0.024)	There was a difference in the adjusted change for weight (kg): -0.20 (95% CI: -0.38 to -0.02; p=0.031) in the children from the intervention arm.
Vinter et al. (2011)	Tanvig et al. (2015)	No difference in randomised group mean: BMI Z-score (C: -0.18 [-0.42;0.05] vs I: 0.06 [-0.17; 0.29]) Percentage of ow or ob children (10.9% vs 6.7%)	The non-significant result may reflect the limited difference in GWG between intervention and control groups

BMI, body mass index; C, control; CI, confidence interval; GDM, gestational diabetes mellitus; GI, glycaemic index; GL, glycaemic load; GWG, gestational weight gain; I, intervention; MET, metabolic equivalent of task; MUA, mid-upper arm; ob, obese; ow, overweight; PA, physical activity; SD, standard deviation; SFA, saturated fatty acids. * Children's BMI were calculated using a Finnish BMI for age calculator for children aged 2–20 years (Saari et al. 2011).

Table 4: Characteristics of the antenatal interventions

Reference	Country	Design	Aims	Outcomes	Study population	Intervention
All BMI Categories						
Walsh et al. (2012) ROLO study	*Ireland*	RCT	To determine if a low GI diet from early pregnancy in a group of women all in their second pregnancies who had previously delivered an infant weighing greater than 4000g.	Primary infant outcome: birth weight. Secondary outcomes: GWG and maternal glucose intolerance.	N = 781 all BMI categories I: n=383 BM I= 26.8 ± 5.1 kg/m^2 C: n=398 BMI=26.8 ± 4.8 kg/m^2 No published ethnicity data	I: Diet only. 1 group dietary session at <18 weeks' gestation. Introduced to principles of study, rationale of low GI diet in pregnancy and provided with written resources for swapping to low GI foods. Further meeting with dietitian to reinforce the low GI diet concept at 28 and 34 weeks gestation. C: Standard antenatal care.
Rauh et al. (2013) FeLIPO study	*Germany*	Cluster-RCT	To determine if counselling, focusing on diet, physical activity and weight monitoring prevents weight gain in excess of IOM guidelines.	Primary maternal outcome: GWG within IOM guidelines.	N=250 all BMI categories I: n=167 BMI: 19.9-23.7 kg/m^2 C: n=83 BMI: 20.6-26.6 kg/m^2 No published ethnicity data	I: Diet and physical activity. Recruited <18week gestation. Two individual counselling sessions in the 20th and 30th week of pregnancy, including nutrition PA and GWG monitoring and personalised feedback on their 7-day food and activity diaries. C: Standard antenatal care.
Kinnunen et al. (2007)	*Finland*	Quasi-RCT	To determine if individual counselling on diet and physical activity during pregnancy can prevent excessive GWG.	Primary maternal outcome: GWG. Secondary outcomes: changes in diet and physical activity and incidence of macrosomia.	N=105 all BMI categories I: n=49 n=8 (17%) BMI ≥ 26 kg/m^2 C: n=56 n=2 (4%) BMI ≥ 26 kg/m^2	I: Diet and physical activity. Individual counseling on PA and diet at 5 routine visits to a maternity health care nurse from 8-9 to 37 weeks gestation Option to attend supervised group PA sessions 1x/week until 37 weeks gestation. Dietary advice included: regular meals, consumption of fruit, vegetables and high fibre bread, restricting sugary snacks. C: Standard antenatal care.

				No published ethnicity data	
Ronnberg et al. (2014)	*Sweden*	RCT	To evaluate if a feasible, low-cost intervention could decrease the percentage of women gaining weight above the IOM recommendations on GWG.	Primary outcome: GWG.	N= 374 all BMI categories I: n = 192 BMI: 25.2 ± 4.9 kg/m^2 C: n= 182 BMI: 25.3 ± 4.8 kg/m^2	I: Physical activity only. Individual education about IOM guidelines for recommended GWG according to BMI category at first antenatal visit. Personalised graphs including recommended interval of GWG were provided. Recommendation of PA during pregnancy; a moderate level of exertion during a total of approximately 30 mins/day. Activities should entail a minimal risk of falling fetal injury. Activities were based on personal interests and abilities. Activities could also be adjusted during pregnancy. C: Standard antenatal care.
Luoto et al. (2011) NELLI study	*Finland*	Cluster-RCT	To determine if lifestyle counselling in pregnant women at high risk of GDM can prevent GDM or macrosomia.	Primary maternal outcome: GDM. Primary infant outcome: birthweight. Secondary outcomes: GWG, insulin treatment during pregnancy.	N=399 all BMI categories I: n=219 BMI: 17.0-48.5 kg/m^2 C: n=180 BMI: 17.2-37.8 kg/m^2 No published ethnicity data	I: Diet and physical activity. Intervention from 8-12 weeks to 37 weeks gestation. Recommendations provided for GWG. PA sessions (from 8-12 weeks gestation) and dietary counselling sessions (from 16-18 weeks) were offered The aims of the sessions were to increase leisure time PA and to adhere to Finnish dietary recommendations regarding the proportions of fats, sugar, fibre, fruit and vegetables. Further PA and dietary counselling subsequently provided at each antenatal visit. C: Standard antenatal care.
Obese only (BMI ≥30 kg/m^2)						
Poston et al. (2015) UPBEAT study	*UK*	RCT	To determine if a dietary and physical intervention could reduce incidence of GDM and macrosomia.	Primary maternal outcome: GDM. Primary infant outcome: macrosomia. Secondary outcomes: dietary measures, physical activity scores, GWG, maternal anthropometric measurements and blood biochemistry.	N = 1555, obese women I: n=783, 36.3 ± 5.0 kg/m^2 C: n=772, 36.3 ± 4.6 kg/m^2 Ethnicity, n (%) White I: 483 (63) C: 490 (63) Black I: 200 (26) C: 202 (26) Asian I: 48 (6) C: 47 (6) Other I: 41 (5) C: 44 (6)	I: Diet and physical activity. Eight health trainer-led group/individual sessions of 1h duration 1x/week over 8 weeks starting between 15-18 weeks gestation - Material covered over phone/email if participant could not personally attend session. Women received advice on strategies used to achieve goals, behavioural change, provided with booklets with recommended foods, recipes and suggestions for physical activity (DVDs of an exercise regimen that was safe for pregnancy, a pedometer, and a log book for recording their weekly goals). The aim was to promote a healthy pattern of eating but not necessarily to restrict energy intake, and tailored to the woman's habitual diet and cultural preference.

					Exchanging carbohydrate-rich foods with a medium-to-high GI for those with a lower GI to reduce the GL was suggested, as was restricting dietary intake of SFA. incremental increases in walking from a pedometer assessed baseline were advised. C: Standard antenatal care.
Vesco et al. (2014) Health Moms Trial	*USA*	RCT	To determine if a weight management intervention can limit GWG in obese pregnant women.	Primary maternal outcome: GWG. Secondary outcomes: weight change at 1 year postpartum, proportion of infants with birth weight>90th percentile for gestational age.	N = 114 obese women I: n=56, 36.7 ± 5.2 kg/m^2 C: n=58, 36.8 ± 4.7 kg/m^2 Ethnicity, n (%) White I: 49(88) C: 49(85)	I: Diet and physical activity. Two weekly individual dietary counselling sessions provided <21 weeks' gestation. Participants attended weekly group meetings until delivery. Daily food and activity diaries were recommended and reviewed weekly. Each group session included: check-in, a nutrition and/or exercise topic, a behaviour change topic, a goal-setting segment for the following week and a plan for how to meet goals. The goals were: to maintain weight within 3% of the original weight (at randomisation), to keep calorie intake within the individual goal, to adopt a sodium-restricting diet and to exercise daily (30 min moderate daily activity/10000 pedometer steps daily). C: Standard antenatal care.
Vinter et al. (2011) LiP Study	*Denmark*	RCT	To study the effects of lifestyle intervention on GWG and obstetric outcomes.	Primary maternal outcomes: GWG, incidence of preeclampsia, pregnancy-induced hypertension, GDM, caesarean section. Primary infant outcomes: macrosomia and NICU admissions.	N = 304 obese women I: n=150, 33.4 kg/m^2 (31.7 – 36.5) C: n=154, 33.3 kg/m^2 (31.7 – 36.9) No published ethnicity data	I: Diet and physical activity. Recruitment from 10-14 weeks. Four individual dietary counselling sessions with trained dietitians to provide a personalised diet. Encouragement to be moderately physically active for 30-60 minutes daily. Free, full-time memberships to a fitness centre. C: Standard antenatal care.

BMI, body mass index; C, control; GDM, gestational diabetes mellitus; GI, glycaemic index; GL, glycaemic load; GWG, gestational weight gain; I, intervention; LiP, lifestyle in pregnancy; NICU, neonatal intensive care unit; PA, physical activity; RCT, randomised controlled trial; UPBEAT, UK pregnancy better eating and activity trial.

Table 5: Impact of antenatal lifestyle intervention on primary and secondary outcomes of the antenatal RCT

Publication	Primary outcomes	Secondary/additional outcomes
		All BMI categories
Walsh et al. (2012)	Infant outcome: No effect on birthweight.	Less GWG in women in the intervention arm (12.2 vs 13.7 kg, p=0.01). Glucose intolerance significantly lower in intervention arm, 21% vs 28% (p=0.02).
Rauh et al. (2013)	Maternal outcome: lower proportion of women exceeding GWG with IOM guidelines from the intervention group (38% vs 60%) (OR: 0.5; 95% CI: 0.3 to 0.9).	Participants in the intervention group gained less weight than those in the control group (-1.7; 95% CI: -3.0 to -0.3; p=0.035), only 17% of women in the intervention showed substantial weight retention (more than 5 kg) at 4-month pp compared to 31% in the control arm. No significant difference in obstetric outcomes.
Kinnunen et al. (2007)	Maternal outcome: No effect on GWG.	Healthier diets maintained in I versus C during pregnancy. There were no macrosomic babies in the intervention group, but eight (15%) in the control group (p=0.006).
Ronnberg et al. (2014)	Maternal outcome: No effect on the proportion of women exceeding the IOM guidelines for GWG (41.1% vs 50.0%, p=0.086).	Difference in mean GWG I: 14.19kg (4.45 SD) C: 15.31kg (5.38 SD).
Luoto et al. (2011)	Maternal outcome: No effect on GDM. Infant outcome: birthweight lower in the intervention than usual care group (3,532±514g *vs* 3,659±455g, p=0.008).	Total GWG, preeclampsia, or use of diabetic medication did not differ between the groups. Women in the intervention group increased intake of fibre (AC 1.83, 95% CI 0.30–3.25, p=0.023) and PUFAs (AC 0.37, 95% CI 0.16–0.57, p=0.001), decreased intake of SFA (AC−0.63, 95% CI −1.12 to −0.15, p=0.01) and intake of saccharose (AC −0.83, 95% CI −1.55 to −0.11, p=0.023), than women in the usual care group.
		Obese only (BMI ≥30 kg/m^2)
Poston et al. (2015)	Maternal outcome: No effect on GDM. Infant outcome: No effect on macrosomia.	Maternal dietary quality, assessed by total energy intake, GI and macronutrient intake all lower in intervention group (p<0.002). PA (p<0.002), GWG (p=0.041) and adiposity, defined as sum of skinfold (p<0.002), were reduced in the intervention group.
Vesco et al. (2014)	Maternal outcome: Between baseline and 34 weeks gestation, intervention participants gained less weight (5.0 vs. 8.4 kg; p<0.001).	Reduced prevalence of LGA in the intervention group compared to the control group (9% vs 26% p=0.02).
Vinter et al. (2011)	Maternal outcomes: Reduction in GWG with intervention compared to control (7.0 vs 8.6 kg; p=0.01). Infant outcome: No significant effect on macrosomia and NICU admissions.	No effect for other obstetric outcomes.

AC, adjusted coefficient; C, control; GDM, gestational diabetes mellitus; GI, glycaemic index; GWG, gestational weight gain; I, intervention; IOM, Institute of Medicine; LGA, large for gestational age; OR, odds ratio; PA, physical activity; pp, post-partum; PUFAs, polyunsaturated fatty acids; RCT, randomised controlled trial; SFA, saturated fatty acids.

Table 6: Sources of bias in offspring follow-ups following antenatal lifestyle interventions in publication order of offspring follow-up

Author	Study design	Randomisation	Allocation	Attrition	Risk of bias
		Follow-up			
Mustila et al. (2012)	Quasi-RCT	HIGH	UNCLEAR	HIGH	HIGH
Rauh et al. (2015)	Cluster-RCT	LOW	LOW	LOW	LOW
Tanvig et al. (2015)	RCT	LOW	LOW	HIGH	LOW
Horan et al. (2016)	RCT	LOW	LOW	HIGH	LOW
Kolu et al. (2016)	Cluster-RCT	LOW	UNCLEAR	HIGH	MODERATE
Vesco et al. (2016)	RCT	LOW	UNCLEAR	HIGH	MODERATE
Patel et al. (2017)	RCT	LOW	LOW	HIGH	LOW
Ronnberg et al. (2017)	RCT	LOW	LOW	LOW	LOW
		Antenatal			
Kinnunen et al. (2007)	Quasi-RCT	HIGH	UNCLEAR	LOW	MODERATE
Rauh et al. (2013)	Cluster-RCT	LOW	LOW	LOW	LOW
Vinter et al. (2011)	RCT	LOW	LOW	LOW	LOW
Walsh et al. (2012)	RCT	LOW	LOW	LOW	LOW
Luoto et al. (2011)	Cluster-RCT	LOW	UNCLEAR	LOW	LOW
Vesco et al. (2014)	RCT	LOW	UNCLEAR	LOW	LOW
Poston et al. (2015)	RCT	LOW	LOW	LOW	LOW
Ronnberg et al. (2014)	RCT	LOW	LOW	LOW	LOW

RCT, randomised controlled trial

Appendix 1: Electronic search criteria

MEDLINE and EMBASE

(1974-4th July 2017)

(P) Patient

#1 pregnancy/
#2 pregancy.mp.
#3 pregnan*.tw.
#4 gestation/
#5 maternal.mp.
#6 weight gain/
#7 exp body composition/
#8 exp body mass index/
#9 body size/
#10 exp animals/ not humans.sh.

(I) Intervention

#11 exp Diet/
#12 Randomi*ed controlled trial.pt
#13 Control* clinical trial.pt
#14 education/ or education.mp.
#15 counceling/ or counseling.mp.
#16 Energy Intake/ or dietary intake.mp.
#17 nutrition* advice/ or diet* advice.mp.
#18 low energy/ or low calorie.mp.
#19 glyc?emic index/ or glyc?emic load.mp.
#20 low carbohydrate.mp.
#21 low fat.mp.
#22 dietitian/ or dietician/ or nutritionist.mp.
#23 dietary assessment/ or dietary report.mp.
#24 diet* recall.mp.
#25 food frequency questionnaire.mp.
#26 food diary/ or food record/ or diet record.mp.
#27 health* eating.mp.
#28 Exp exercise/
#29 Physical therapy/ or physical activity.mp

(O) Outcomes

#30 Exp child/
#31 Exp infant/
#32 Child*/ or infan*.mp
#33 Follow?up.mp
#34 Body mass index/

#35 Obesity/ or exp pediatric obesity/

#36 Exp body weights and measures/

(C) Combination

#37 #1 OR #2 OR #3 OR #4 OR #5

#38 #6 OR #7 OR #8 OR #9

#39 #11 OR #12 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29

#40 #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36

#41 #37 AND #38 AND #39 AND #40

#42 #41 NOT #10

#43 Limit #42 to yr=1990:current

Articles cited in MEDLINE: 2967

Articles cited in EMBASE: 218

Cochrane CENTRAL Register of Controlled Trials

#1 pregnan*

#2 gestation

#3 weight gain

#4 body mass index

#5 randomised controlled trial

#6 diet

#7 lifestyle

#8 physical activity

#9 intervention

#10 Infant

#11 child

#12 body composition

#13 animal not human

#14 #1 OR #2

#15 #3 OR #4

#16 #5 OR #6 OR #7 OR #8 OR #9

#17 #10 OR #11 OR #12

#18 #14 AND #15 AND #16 AND #17

#19 #18 NOT #13

Articles cited in Cochrane: 380